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Leukaemia Section

Short Communication

t(11;19)(q23;p13) KMT2A/MYO1F

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Abstract

Review on t(11;19)(q23;p13), with data on clinics, and the genes involved.

KEYWORDS
Chromosome 11; Chromosome 19; KMT2A; MYO1F; Acute myeloid leukemia

Clinics and pathology

Disease

Acute myeloid leukemia

Phenotype/cell stem origin

Seven cases are available, six of them were infant patients. Two were diagnosed with acute monocytic leukemia (AMoL) (Taki et al., 2005; Duhoux et al., 2011). There were also 4 other cases of infant AML, not otherwise specified (NOS) (Lo Nigro et al., 2002; Meyer et al. 2013) and 1 pediatric AML-NOS (Meyer et al. 2013).

Epidemiology

In the large study by Meyer et al., 2013, the four cases (3 infant AML, 1 pediatric AML) were part of a series of 692 infant ALL, 160 infant AMLs, 339 pediatric AMLs, 313 pediatric ALLs, 415 adult ALLs and 373 adult AMLs. This chromosome abnormality seems so far restricted to a subset of patients: extremely young patients with a diagnosis of AML.

Clinics

One patient was diagnosed at birth (Duhoux et al., 2011), and another one at 2 months of age (Taki et al., 2005).

Prognosis

Scarce data: one patient died 5 days after admission (Taki et al., 2005).

Cytogenetics

Cytogenetics morphological

The t(11;19)(q23;p13.3) was the sole abnormality in the case described by Duhoux et al., 2011, while the cases of Lo Nigro et al., 2002 and Taki et al., 2005 were complex translocations.

Genes involved and proteins

KMT2A (myeloid/lymphoid or mixed lineage leukemia)

Location
11q23.3

DNA/RNA
37 exons, spanning about 120 kb; 13-15 mRNA

Protein
3969 amino acids, 431 kDa; Transcriptional regulatory factor. MLL is known to be associated with more than 30 proteins, including the core components of the SWI/SNF chromatin remodeling

complex and the transcription complex TFIID. MLL binds promotors of HOX genes through acetylation and methylation of histones. MLL is a major regulator of hematopoesis and embryonic development, through regulation of HOX genes expression regulation (HOXA9 in particular).

MYO1F

Location

19p13.2

DNA/RNA

28 exons, 3297 nucleotides

Protein

1,098 amino acids; 124 KDa; Myosins are a large family of ATP-driven mechanoenzymes. MYO1F belong to myosin class I, which includes myosins that are able to interact with actin filaments and lipid membranes. Presence of three tail homology regions (TH1, TH2 and a SH3 domain named TH3). These "long-tailed" myosins (i.e. with additional TH2 and TH3) are able to crosslink actin filaments via the TH2 domain and generate mechanical activities using the actin cytoskeleton as a tract. MYO1F contains a myosin motor domain (amino acids 17 - 690); this motor domain contains an actin binding site. It has an ATPase activity/cycle with association/dissociation of myosin with actin. The motor domain is followed by an IQ domain (isoleucine/glutamine motifs, aa 693 - 722), and a TH1 domain (Tail Homology domain, aa 728 - 917). TheTH1 domain is responsible for membrane interaction and, within TH1, a pleckstrin homology PH domain which is a negatively charged phospholipids -binding motif. There are several phosphosites located in the TH2 domain, required for binding to microtubules and microfilaments. TH2 is alanine and proline-rich (aa 941 - 1000). The C-terminus is a SH3 domain (SRC Homology 3 domain, aa 1041 - 1098); it should mediate assembly of specific protein complexes via binding to proline-rich peptides. TLR4 activation induces phosphorylation of MYO1F. MYO1F is a cytosolic protein predominantly expressed in the immune system (Wenzel et al., 2015; Walklate et al., 2016).

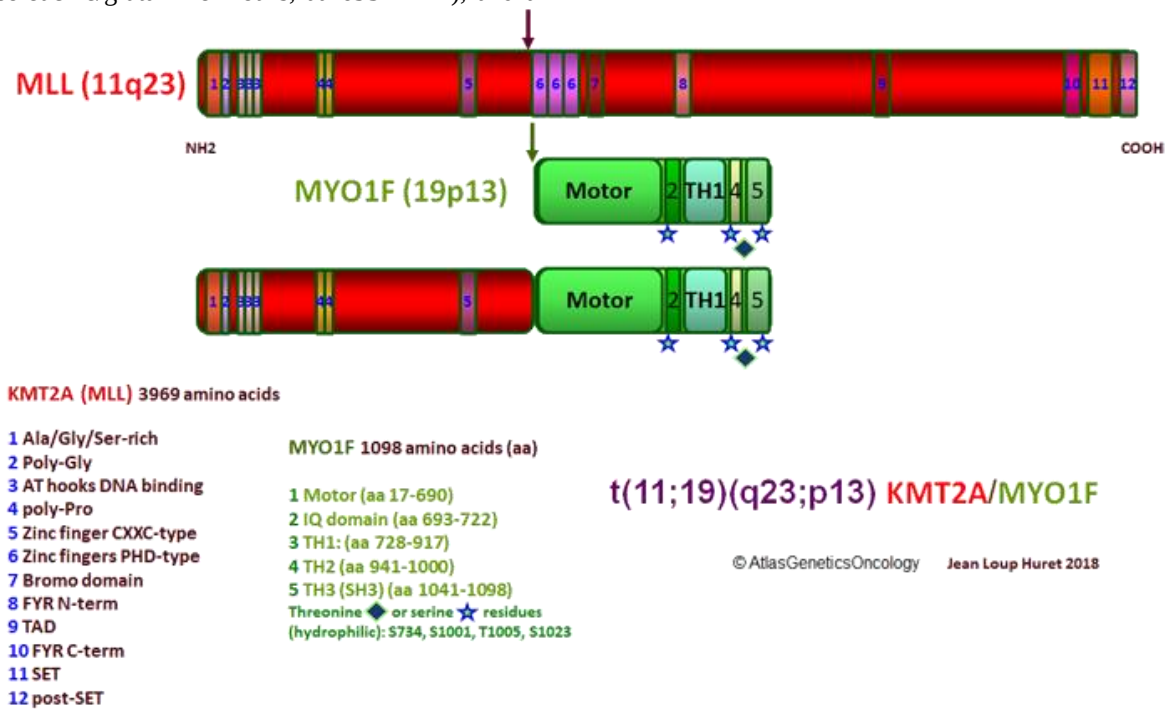
Result of the chromosomal anomaly

Hybrid gene

Description

KMT2A exon 9 was fused to MYO1F exon 2; the breakpoint was thus located within MLL intron 9 in the cases reported by Taki et al., 2005 and Duhoux et al., 2011. The breakpoint in KMT2A was in intron 10 in cases studied by Meyer et al. 2013.

Fusion protein



KMT2A_MYO1F fusion protein, with AT hooks, zinc fingers CXXC type from KMT2A in N-terminus, fused to the entire MYO1F protein in C-terminus.

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